438. *The Preparation of Amino-alcohols. Part I.*

By JOHN T. ABRAMS and FREDERIC S. KIPPING.

THE object of the work, a part of which is described in this paper, was the preparation of aromatic amino-alcohols containing a side chain, $CH(OH)\cdot CRR'\cdot NH_2$, similar to that present in adrenaline. Such compounds have already been obtained by the following methods: (a) The interaction of halogenohydrins, $Ar\cdot CH(OH)\cdot CH_2X$, and ammonia (Tiffeneau, *Compt. rend.*, 1907, **145**, 811; Böttcher, *Ber.*, 1909, **42**, 253; Mannich, Neumann, and Jacobsohn, *Arch. Pharm.*, 1910, **248**, 127); the disadvantages of this process are that it is sometimes very difficult to prepare the hydrins themselves in a pure state (Pauly and

Neukam, *Ber.*, 1908, **41**, 4151), but more particularly that, owing to the intermediate formation of oxides, structural isomerides of the desired bases are sometimes formed (Mannich, Neumann, and Jacobsohn, *loc. cit.*; Levy and Sfiras, *Compt. rend.*, 1930, **191**, 261).

(b) The action of ammonia or an amine on compounds of the type $Ar{\cdot}CO{\cdot}CH_2X$, formed from aromatic substances and halogenated fatty acids or acyl chlorides (Dzierzgowski, *J. Russ. Phys. Chem. Soc.*, 1893, **25**, 275; Ott, *Ber.*, 1926, **59**, 1068), and the subsequent reduction of the amino-ketone by a suitable process, usually catalytic (Hoshino and Kaisha, Jap. Pat. 42351; Hyde, Browning, and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2287). This method has been applied specially to the halogen acyl compounds obtained from phenols, phenolic ethers (Mannich, Neumann, and Jacobsohn, *loc. cit.*), and dichlorobenzene (Glynn and Linnell, *Pharm. J.*, 1932, **129**, 249), in which process much tarry matter is often formed, although work on the intermediate products in the case of phenols, and on the effect of various catalysts, has partly overcome this difficulty. Other disadvantages of this method are the difficulty of preparing acids of the type $CRR'X{\cdot}CO_2H$, the instability of some of the amino-ketones (Tutin, J., 1910, **97**, 2495), and, in the case of certain phenolic ethers, the elimination of the alkylamino-group during the dealkylation of the methoxy-radical.

(c) The reduction of cyanohydrins, catalytically or otherwise (Wolfheim, *Ber.*, 1914, **47**, 1448; D.R.-P. 193,634; Buck, *J. Amer. Chem. Soc.*, 1933, **55**, 2593, 3388; Harting and Munch, *ibid.*, 1928, **50**, 3370). This method is limited to the formation of bases of the type $Ar{\cdot}CH(OH){\cdot}CH_2{\cdot}NH_2$, and the yields are sometimes low: further, in many cases, during catalytic reduction the hydroxyl group is displaced by hydrogen.

(d) The condensation of aminoacetals with phenols or phenolic ethers in the presence of hydrogen chloride (Hinsberg, *Ber.*, 1923, **56**, 852), in which process monohydric phenols usually react mainly as in (I) and polyhydric phenols as in (II).

(I.) $2Ph{\cdot}OH + CH(OEt)_2{\cdot}CH_2{\cdot}NH_2 + HCl \longrightarrow (HO{\cdot}C_6H_4)_2CH{\cdot}CH_2{\cdot}NH_2,HCl + 2EtOH$

(II.) $C_6H_3(OH)_3 + CH(OEt)_2{\cdot}CH_2{\cdot}NH_2 + HCl \xrightarrow{H_2O} C_6H_2(OH)_3{\cdot}CH(OH){\cdot}CH_2{\cdot}NH_2,HCl + 2EtOH$

No extension of this method to side-chain homologues of such compounds seems to have been recorded.

(e) The condensation of aldehydes with nitromethane (Rosenmund, *Ber.*, 1913, **46**, 1034; Nagai, Brit. Pat. 118,298) or its homologues (Nagai and Kanao, *Annalen*, 1929, **470**, 157) and the reduction of the products: in this process the nitro-alcohol sometimes loses the elements of water.

In the present paper there are described syntheses which start from ethyl benzoylacetate and proceed as follows:

$$COPh{\cdot}CH_2{\cdot}CO_2Et \longrightarrow COPh{\cdot}CHR{\cdot}CO_2Et \longrightarrow COPh{\cdot}CHR{\cdot}CO{\cdot}NH_2 \longrightarrow CHPh(OH){\cdot}CHR{\cdot}CO{\cdot}NH_2 \longrightarrow CHPh(OH){\cdot}CHR{\cdot}NH_2$$

Experimental.

Preparations of ethyl benzoylacetate carried out exactly as described by Claisen (*Annalen*, 1896, **291**, 71), and collected from 167—170°/18—19 mm. gave yields of 70—72% of the theoretical, calculated from the weight of the ethyl sodioacetylbenzoylacetate; Claisen gives 75—79·4% and the optimum yield recorded by Shriner and Schmidt (*J. Amer. Chem. Soc.*, 1929, **51**, 3636) is 78·1%. The criticisms by these authors of Claisen's work are therefore unfounded.

Ethyl α-benzoylpropionate (b. p. 150—153°/12 mm.), ethyl α-benzoylbutyrate (b. p. 169—173°/19 mm.), and ethyl α-benzoyl*iso*butyrate (b. p. 167—171°/18 mm.) were obtained from the corresponding acetate in yields of 72, 68, and 50% respectively of the theoretical; in the last preparation the sodium derivative of the benzoyl propionate was formed by treating the ester with sodium suspended in toluene. These results confirm those of Perkin and Calman (J., 1886, **49**, 156), and Perkin and Hope (J., 1909, **95**, 2043), and show that the criticisms of Dorsch and McElvain (*J. Amer. Chem. Soc.*, 1932, **54**, 2960) of this work of Perkin and his colleagues are unwarranted.

Benzoylacetamide was obtained from the ester (30 g.) in yields of 80—81% of the theoretical by using aqueous ammonia (400 c.c., *d* 0·88) and acacia gum (0·5 g.) and shaking vigorously during 4 hours; the emulsion was then kept during 6 days and shaken each day during an hour. The yellowish crystalline product, β-imino-β-phenylpropionamide, boiled with water, gave the pure amide, m. p. 112—113° as stated by Guareschi (Beilstein's " Organische Chemie," Vol. X, p. 679).

α-Benzoylpropionamide was prepared from the corresponding ester (14 g.), aqueous ammonia (320 c.c., *d* 0·88), and acacia gum (1 g.), the mixture being shaken during 2½ hours and the crystals collected after 3 days. The amide (yield, 67%) crystallised from alcohol in lustrous rhomboidal plates, m. p. 153° (Found : C, 67·8; H, 6·2; N, 7·8. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2; N, 7·9%).

Dorsch and McElvain (*loc. cit.*) give m. p. 145—146°.

α-Benzoylbutyramide separated very slowly in colourless needles when the corresponding ester (10 g.) was shaken with aqueous ammonia (250 c.c., *d* 0·88) and acacia gum (1 g.). The amide, collected after 10 days and recrystallised from alcohol or acetone, melted at 155° (yield, about 42%) (Found : C, 69·0; H, 6·6; N, 7·2. Calc. for $C_{11}H_{13}O_2N$: C, 69·1; H, 6·8; N, 7·3%). Dorsch and McElvain (*loc. cit.*) give m. p. 148—149°. No imine was detected during the above preparation and attempts to obtain it by treating the amide with dry ammonia in benzene solution in the presence of anhydrous sodium sulphate were unsuccessful.

Ethyl α-benzoyl*iso*butyrate could not be converted into the amide by the above method; even after a month's time a large proportion of the oil was unchanged and the only crystalline product was benzamide.

In such reactions one α-alkyl group seems to prevent the formation of the corresponding imine, and two α-alkyl groups, the formation of the amide. This is in harmony with the observations of Perkin and Calman, who found it possible to hydrolyse the methyl and ethyl derivatives of ethyl benzoylacetate by using 3% potash solution, but could not obtain the corresponding disubstituted acids in a similar manner.

β-Hydroxy-β-phenylpropionamide was obtained by reducing benzoylacetamide in aqueous alcoholic solution with amalgamated aluminium foil; after filtration and evaporation the product, recrystallised from alcohol, melted at 118—119° (yield, about 44%).

β-Hydroxy-β-phenyl-α-methylpropionamide was prepared by reducing α-benzoylpropionamide (6·2 g.) in warm alcohol (100 c.c.) and water (20 c.c.) with amalgamated aluminium foil (4·4 g.); the necessary quantity of foil was determined by measuring the evolved hydrogen and comparing its volume with that of the gas obtained in a blank experiment. The greenish-yellow oil obtained on evaporation began to crystallise when treated with a little ethyl acetate; the solid, recrystallised from ethyl acetate–light petroleum, gave an apparently homogeneous product (2 g.) in rhomboidal plates, m. p. 134—135° (Found : C, 66·7; H, 7·35. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The rest of the product remained as a viscous oil.

β-Hydroxy-β-phenyl-α-ethylpropionamide was prepared similarly (α-benzoylbutyramide, 3·4 g.; alcohol, 60 c.c.; water, 15 c.c.; aluminium amalgam, 1·8 g.). The yellowish glue-like product (3 g.) was dissolved in ethyl acetate and fractionally precipitated with light petroleum; after many operations the more sparingly soluble fractions afforded a pure substance, m. p. 134—135°, which crystallised in needles and was readily soluble in hot acetone and alcohol, sparingly in ether and benzene (Found : C, 68·1; H, 7·6. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%).

From the more soluble fractions a very small quantity of another compound, probably the diastereoisomeride, was obtained in needles, m. p. 128—131°; the rest of the product was crystalline but was obviously a mixture, melting below 110°.

β-Amino-α-phenylethyl Alcohol.—A suspension of β-hydroxy-β-phenylpropionamide (3·75 g.) in water (40 c.c.) was slowly treated below 0° with hypobromite solution (bromine, 3·5 g.; sodium hydroxide, 1·8 g.; water, 10 c.c.). A pale yellow substance was formed and after 15 minutes a solution of sodium hydroxide (2·7 g.) in water (30 c.c.) was added, the final temperature being 8°. The mixture was left at 10° for 2 hours, and benzoyl chloride then added in excess, alternately with sodium hydroxide solution. The precipitated benzoyl derivative (2·8 g.), after recrystallisation from alcohol, had m. p. 146—148°. In other experiments the base was isolated as the hydrochloride by extracting the alkaline solution with chloroform and passing dry hydrogen chloride into the dried extract : the pure salt melted at 175—177° (cf. Wolfheim, *Ber.*, 1914, **47**, 1448).

β-Amino-α-phenylpropyl Alcohol.—β-Hydroxy-β-phenyl-α-methylpropionamide (1·1 g.), as a fine paste with water (12 c.c.), was slowly added to well-stirred hypobromite (bromine, 0·33 c.c.; sodium hydroxide, 1·2 g.; water, 10 c.c.) at — 7°. The mixture was allowed to reach room

temperature and sodium hydroxide (0·6 g.), dissolved in water (3 c.c.), was then added; after 2 hours, lustrous plates separated. This product, recrystallised from ethyl acetate, gave stout well-defined prisms (0·66 g.), m. p. 116—117°, which contained halogen and doubtless consisted of the bromoamide. The aqueous filtrate was repeatedly extracted with chloroform, and dry hydrogen chloride passed into the dried solution. The hydrochloride of *dl*-nor*iso*ephedrine (0·22 g.) was thus obtained in needles, m. p. 169—170°. The halogen compound, m. p. 116—117°, could be recrystallised unchanged from hot water or alcohol and even when warmed with a 13% solution of sodium hydroxide during about 20 minutes at 60°, seemed to undergo very little change; in the course of a further 60 minutes, however, decomposition appeared to be complete. The base, extracted with chloroform, gave 0·25 g. of the hydrochloride, a yield of 70·4% calculated from the bromoamide. The total yield calculated from the weight of the amide was 50·7%.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, August 28th,* 1934.]